MSK PROTOCOL COVER SHEET

A Phase 1/2 study of combination osimertinib and bevacizumab as treatment for patients with EGFR-mutant lung cancers

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1.0 PROTOCOL SUMMARY AND/OR SCHEMA

Study Title:	A Phase 1/2 study of combination Osimertinib and bevacizumab as treatment for patients with EGFR-mutant lung cancers
Study Objectives:	**Phase 1:** Primary Objective: To determine the maximum tolerated dose of combination Osimertinib and bevacizumab in patients with untreated EGFR-mutant lung cancers. **Phase 2:** Primary Objective: Assess the progression-free survival at 12 months of combination Osimertinib and bevacizumab in patients with untreated EGFR-mutant lung cancers. Secondary Objectives: 1) Measure overall response rate (CR+PR), 2) measure progression-free survival 3)measure intracranial progression-free survival 4) measure overall survival 5) further define the toxicity profile of the combination **Correlative Studies:** Objectives: 1) to identify EGFR T790M in pre and post treatment samples and correlate with PFS on Osimertinib and bevacizumab 2) perform next-generation sequencing based mutation testing on tumors before treatment and at progression.
Patient Population:	Patients with locally advanced or metastatic lung adenocarcinomas with a confirmed EGFR mutation not yet treated with an EGFR TKI.
Number of patients:	Phase 1: Maximum of 12 patients Phase 2: Maximum of 46 patients (including 6 from the phase 1)
Inclusion Criteria:	All patients must have: • Written informed consent • Advanced biopsy-proven metastatic non-small cell lung cancer • Somatic activating mutation in EGFR • No prior treatment with an EGFR TKI. • No prior treatment with a VEGF inhibitor. • Measurable (RECIST 1.1) indicator lesion not previously irradiated • Karnofsky performance status (KPS) ≥ 70% • Age >18 years old

Exclusion Criteria:	Patients are to be excluded from the study if they meet any of the following criteria: • Any contra-indications to bevacizumab as per the investigator's discretion. Possible contra-indications include but are not limited to recent thromboembolic disease, severe uncontrolled hypertension (systolic blood pressure ≥180 mmHg and/or diastolic blood pressure ≥ 120mmHg), cardiovascular disease, risk of bleeding, hemorrhagic brain metastases, history of severe proteinuria (urine dipstick ≥ 2+ or 24 hr urine > 2gm/24hr)) • Pregnant or lactating women • Any type of systemic anticancer therapy (chemotherapy or experimental drugs) within 2 weeks of starting treatment on protocol. • Any major surgery within 4 weeks of starting treatment on protocol. • Any radiotherapy within 1 week of starting treatment on protocol. • Any evidence of clinically significant interstitial lung disease • Any other condition that, in the opinion of the investigator, may compromise the safety of the patient, or would preclude the patient from successful completion
Study drug:	Osimertinib (also known as AZD9291)and bevacizumab

Study Design:

Phase 1:
This portion of the study will assess whether combination Osimertinib and bevacizumab given at the doses below is safe and tolerable. Osimertinib and bevacizumab have non-overlapping toxicity profiles and we expect that we will be able to utilize the full doses of both agents. A 3+3 dose-escalation design will be utilized.

Three patients will be enrolled at a dose level and assessed for dose limiting toxicities (DLTs) for 1 full cycle (21 days). Toxicity will be graded according to NCI CTCAE version 4. If 2 or more patients develop a DLT at dose level 1, we will de-escalate and utilize dose level -1. If 2 or more patients develop a DLT at dose level -1, we will review toxicity and consider alternative dosing through a protocol amendment.

The MTD (maximum tolerated dose)/recommended phase 2 dose will be the highest dose level at which $\leq$1 DLT is detected in the first cycle for 6 treated patients. If only 3 patients are treated at a dose level being considered for the MTD, an additional 3 patients will be enrolled.

Table 1: Dose levels

Dose level	Osimertinib	Bevacizumab
-1	40mg daily	15mg/kg every 3 weeks
1	80mg daily	15mg/kg every 3 weeks

Phase 2:
Once the phase 1 portion of the study has been completed, patients will be enrolled in the phase 2 portion of the single-arm study of Osimertinib and bevacizumab. A cycle will be 21 days in length. Osimertinib will be dosed daily and bevacizumab is dosed once every 3 weeks. Response to therapy will initially be assessed by interval imaging every 3 cycles of treatment with CT scan of the chest/abdomen/pelvis with response evaluated by RECIST 1.1. An additional 40 patients (for a total of 46) will be enrolled at the MTD. The six patients treated at the MTD in the phase 1 will be included in the phase 2 study.

Correlative studies:
Molecular testing will be performed on archived pre-treatment tumor specimens. A rebiopsy at the time of clinical progression on EGFR TKI will not be mandated per protocol, but is typically done as per standard of care.

EGFR T790M is routinely identified in tumor tissue by several standard methods including a mass spectrometry based mutation platform (Sequenom), locked nucleic acid based PCR sequencing or by next generation sequencing. Our next-generation sequencing based mutation platform (IMPACT) will be performed to compare the molecular alterations in pre and post treatment specimens. The sequencing data will be analyzed for base mutations, insertions, deletions, copy number alterations and

genomic rearrangements in all target genes.

2.0 OBJECTIVES AND SCIENTIFIC AIMS

Phase 1:
Primary Objective: To determine the maximum tolerated dose of combination Osimertinib and bevacizumab in patients with untreated EGFR-mutant lung cancers.

Phase 2:
Primary Objective: Assess the progression-free survival at 12 months of combination Osimertinib and bevacizumab in patients with untreated EGFR-mutant lung cancers.
Secondary Objectives: 1) measure overall response rate (CR+PR), 2) measure progression-free survival 3) measure intracranial progression-free survival 4) measure overall survival 5) further define the toxicity profile of the combination

Correlative Studies:
Objectives: 1) to identify EGFR T790M in pre and post treatment samples 2) perform next-generation sequencing based mutation testing on tumors before treatment and at progression.

3.0 BACKGROUND AND RATIONALE

EGFR-mutant lung cancers
Twenty percent of patients with metastatic lung adenocarcinoma have somatic activating mutations in the epidermal growth factor receptor gene (EGFR). Patients with EGFR-mutant lung adenocarcinomas have a 70% response rate to first-line EGFR-TKI therapy (erlotinib or afatinib) and a median progression-free survival of 9-12 months.(1) First-line EGFR TKI therapy is superior to cytotoxic chemotherapy and is recommended as first-line treatment for patients with EGFR-mutant lung cancers. All patients will develop resistance to EGFR TKI therapy and clinical progression. The majority of patients acquire a second mutation, EGFR T790M, as their dominant mechanism of resistance.(2)

Third-generation EGFR TKIs
There are several EGFR T790M inhibitors in clinical development including Osimertinib.(3) These agents were initially tested in the acquired resistance setting, after progression on first-line, first- generation EGFR tyrosine kinase inhibitors. The overall response rate to Osimertinib in patients who harbor EGFR T790M in their lung cancers is 61% and the overall response rate in all patients was 51%. Osimertinib inhibits mutant EGFR selectively over wild-type EGFR, and avoids significant wild- type EGFR toxicity. The most frequent adverse events seen with Osimertinib in the phase 1 study include diarrhea (47%), rash (40%), nausea (22%) and decreased appetite (21%). The side effect profile is mild and comparable to what is seen with erlotinib. Treatment with erlotinib in BR.21 had an adverse event profile (all grades) that included fatigue (79%), rash (76%), anorexia (69%), diarrhea (55%), and nausea (40%). In contrast, osimertinib had an adverse event profile (all grades) that included diarrhea (47%), rash (40%), nausea (22%), anorexia (21%), and fatigue (17%). Osimertinib received accelerated approval in November 2015, for the treatment of patients with NSCLC with EGFR T790M mutation who have progressed on a previous EGFR TKI. The FDA approved dose of osimertinib is 80mg orally once daily.

Due to its efficacy and tolerable side effect profile, Osimertinib is beginning evaluation as first-line therapy

for patients with EGFR-mutant lung cancers (NCT02296125). FLAURA is a first line study randomizing patients to either Osimertinib versus erlotinib or gefitinib; the primary endpoint of the study is progression free survival. In addition, there was a first line cohort in the AURA study of patients who received osimertinib as first-line treatment for metastatic EGFR-mutant lung cancer. Interim data was presented at ASCO in 2015; 60 patients were treated. The overall response rate was 73%. The median progression-free survival was not yet reached, but 72% of patients (95% CI 55%-84%) were progression-free at 12 months.

Use of VEGF inhibitors in lung cancers

Rational combinations of targeted therapies have been constantly assessed in order to improve patient outcomes. Pro-angiogenesis pathways have been an important therapeutic target as they are essential for tumor growth and metastases. The best characterized pro-angiogenesis pathway is vascular endothelial growth factor (VEGF) signaling pathway. Several studies have demonstrated improved overall survival with the addition of VEGF inhibitors to standard cytotoxic chemotherapies in non-small cell lung cancers.(4-6) Recent studies have combined VEGF inhibitors (bevacizumab, ramucirumab and nintedanib) with first-line and second-line chemotherapy and demonstrated improvements in overall survival. Avastin is approved in non-small cell lung cancer for combination use with cytotoxic chemotherapy. The FDA approved dose of bevacizumab is 15mg/kg given once every 3 weeks.

Preliminary data/Feasibility

EGFR TKI and bevacizumab

The combination of erlotinib and bevacizumab was first-tested after progression on first-line platinum based therapy in molecularly unselected patients. These studies did not meet their primary endpoint but a subgroup analysis suggested that in patients with EGFR-mutant lung cancer, the combination of erlotinib and bevacizumab improved progression free survival compared to erlotinib alone (7, 8). Based on this data, a phase 2 study in Japan randomized untreated patients with EGFR-mutant lung cancers to erlotinib or erlotinib plus bevacizumab with a primary endpoint of progression-free survival (PFS). The median PFS was 16.0 months on the combination compared to 9.7 months with erlotinib alone, HR 0.54, 95% CI 0.36-0.79, p=0.0015(9). Higher incidences of hypertension, bleeding and proteinuria were seen in the patients that received bevacizumab and erlotinib compared to erlotinib alone. A separate single-arm phase 2 was conducted in Japan that assess the combination of gefitinib and bevacizumab as first-line therapy in patients with advanced NCLC harboring EGFR mutations(10). The objective response rate was 73.8% and the median PFS was 14.4 months. The PFS on the study was 4 to 50 months longer with bevacizumab and gefitinib compared to historical EGFR TKI monotherapy(11-14). Both studies, erlotinib plus bevacizumab and gefitinib plus bevacizumab, treated patients with full, FDA-approved doses of both agents, in large part due to their non-overlapping toxicity profiles.

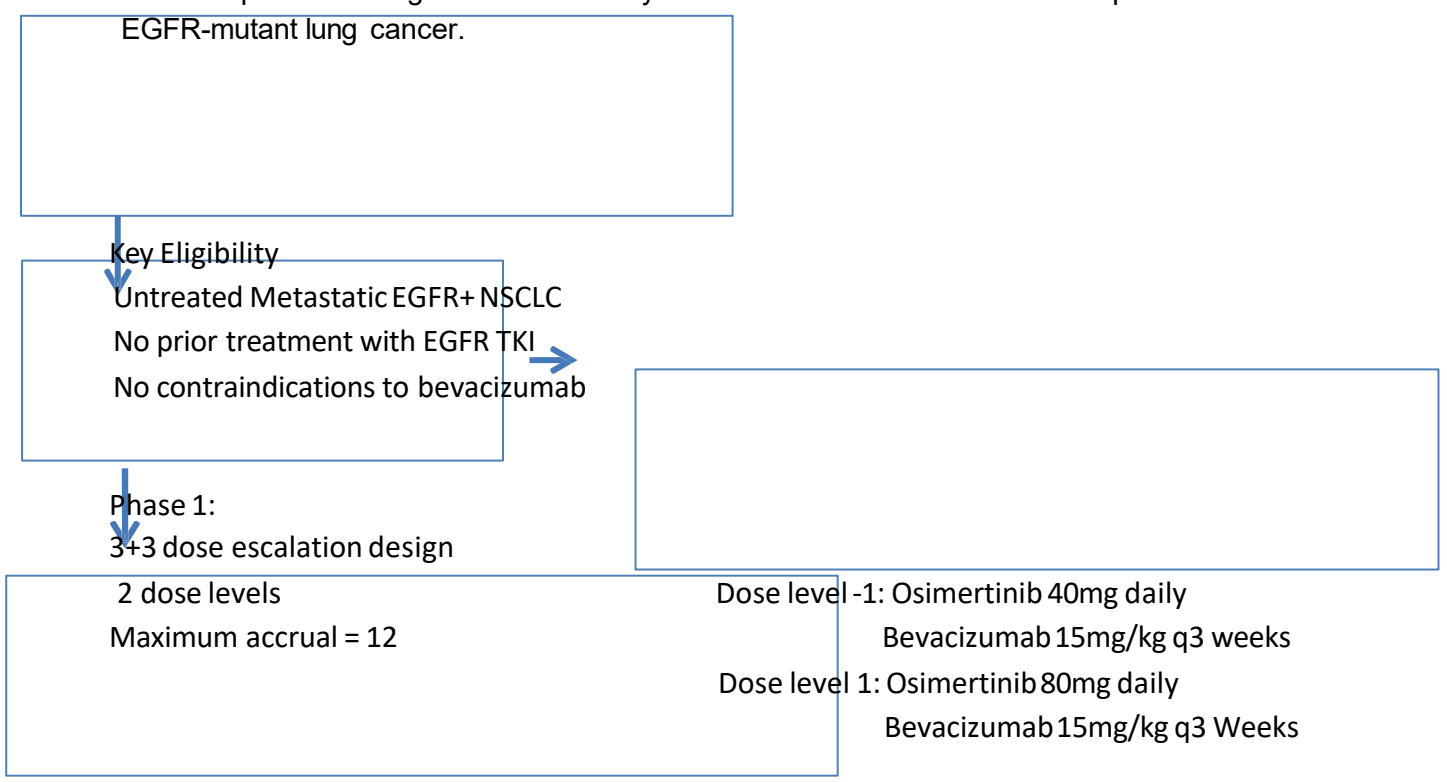
Innovation

First-line Osimertinib has the potential to extend progression free survival for patients with EGFR- mutant lung cancers. As the addition of bevacizumab to erlotinib or gefitinib appears to significantly improve outcomes, the intuitive next study is to combine Osimertinib and bevacizumab in the first- line setting. We will perform a phase 1/2 to further assess toxicity and preliminary efficacy of osimertinib and bevacizumab in the first line setting in patients with EGFR mutant lung cancers. Due to largely non-overlapping toxicity profiles, we will treat patients and full, FDA-approved doses of both agents and allow for a step-down dose level -1 if the dose level 1 is not well tolerated.

4.1 OVERVIEW OF STUDY DESIGN/INTERVENTION

4.2 Design

This is a phase 1/2 single institution study of Osimertinib and bevacizumab in patients with EGFR-mutant lung cancer.



4.3 Intervention

Phase 1:
This portion of the study will assess whether combination Osimertinib and bevacizumab given at the doses below is safe and tolerable. Osimertinib and bevacizumab have non-overlapping toxicity profiles and we expect that we will be able to utilize the full doses of both agents. A 3+3 dose-escalation design will be utilized.

Three patients will be enrolled at a dose level and assessed for dose limiting toxicities (DLTs) for 1 full cycle (21 days). Toxicity will be graded according to NCI CTCAE version 4. If 2 or more patients develop a DLT at dose level 1, we will de-escalate and utilize dose level -1. If 2 or more patients develop a DLT at dose level -1, we will review toxicity and consider alternative dosing through a protocol amendment.

The MTD (maximum tolerated dose)/recommended phase 2 dose will be the highest dose level at which ≤1 DLT is detected in the first cycle for 6 treated patients. If only 3 patients are treated at a dose level being considered for the MTD, an additional 3 patients will be enrolled.

Table 1: Dose levels

Dose level	Osimertinib	Bevacizumab
-1	40mg daily	15mg/kg every 3 weeks
1	80mg daily	15mg/kg every 3 weeks

Phase 2:
Once the phase 1 portion of the study has been completed, patients will be enrolled in the phase 2 portion of the single-arm study of Osimertinib and bevacizumab. A cycle will be 21 days in length. Osimertinib will be dosed daily and bevacizumab is dosed once every 3 weeks. Response to therapy will initially be assessed by interval imaging every 3 cycles of treatment with CT scan of the chest/abdomen/pelvis with response evaluated by RECIST 1.1. An additional 40 patients (for a total of 46) will be enrolled at the MTD. The six patients treated at the MTD in the phase 1 will be included in the phase 2 study.

Correlative studies:
Molecular testing will be performed on archived pre-treatment tumor specimens. A rebiopsy at the time of clinical progression on EGFR TKI will not be mandated per protocol, but is typically done as per standard of care.

EGFR T790M is routinely identified in tumor tissue by several standard methods including a mass spectrometry based mutation platform (Sequenom), locked nucleic acid based PCR sequencing or by next generation sequencing. Our next-generation sequencing based mutation platform (IMPACT) will be performed to compare the molecular alterations in pre and post treatment specimens. The sequencing data will be analyzed for base mutations, insertions, deletions, copy number alterations and genomic rearrangements in all target genes.

5.0 THERAPEUTIC/DIAGNOSTIC AGENTS

5.1 Osimertinib

Osimertinib will be provided by Astra Zeneca. Osimertinib is a crystalline powder presented for oral administration as a beige, film- coated tablet containing either 40mg or 80mg of Osimertinib. Osimertinib beige film-coated tablets contain Osimertinib mesylate, mannitol, microcrystalline cellulose, low-substituted hydroxypropyl cellulose and sodium stearyl fumarate. Tablets will come in high-density polyethylene (HDPE) bottles with child-resistant closures. Tablets should be stored in their original packaging at room temperature. Osimertinib is administered as a once daily dose (fasting). Patients will be required to fast (can take with water only) for at least one hour prior to taking a dose until two hours post-dose.

5.2 Bevacizumab

Bevacizumab will be supplied by Genentech. Bevacizumab is a humanized monoclonal antibody that binds all five isoforms of human VEGF. It is FDA approved for the treatment of metastatic non-squamous, non-small cell lung cancers. It is a recombinant human antibody consisting of 93% human and 7% murine amino acid sequences. Bevacizumab is supplied as a clear to slightly opalescent, sterile liquid ready for parenteral administration. Each 400mg (25mg/mL- 16 mL fill) glass vial contains bevacizumab with phosphate, trehalose, polysorbate 20 and sterile water for injection, USP. Bevacizumab should be stored in the refrigerator (2-8 degrees Celsius) and should be refrigerated until just prior to use. Bevacizumab is administered intravenously every 3 weeks. It can be given irrespective of fasting or fed state. Bevacizumab will be prepared and administered per institutional guidelines outlined in section 9.1.2.

6.1 CRITERIA FOR SUBJECT ELIGIBILITY

6.2 Subject Inclusion Criteria

- Written informed consent
- Advanced biopsy-proven metastatic non-small cell lung cancer
- Somatic activating mutation in EGFR
- No prior treatment with an EGFR TKI.
- No prior treatment with a VEGF inhibitor.
- Measurable (RECIST 1.1) indicator lesion not previously irradiated
- Karnofsky performance status (KPS) ≥ 70%
- Age >18 years old
- Adequate organ function
    - AST, ALT ≤ 3 x ULN
    - Total bilirubin ≤ 1.5x ULN
    - Creatinine ≤ 1.5x ULN OR calculated creatinine clearance ≥ 60ml/min
    - Absolute neutrophil count (ANC) ≥ 1000 cells/mm^3
    - Hemoglobin≥8.0 g/dL
    - Platelets ≥100,000/mm^3

6.3 Subject Exclusion Criteria

- Any contra-indications to bevacizumab which include but are not limited to recent
    1. Any previous venous thromboembolism > NCI CTCAE Grade 3
    2. Severe uncontrolled hypertension (systolic blood pressure ≥150 mmHg and/or diastolic blood pressure ≥100mmHg)
    3. Cardiovascular disease including stroke of myocardial infarction ≤6 months prior to study enrollment, New York Heart Association Grade 2 or greater congestive heart failure, serious cardiac arrythmia uncontrolled by medication
    4. Hemorrhagic brain metastases. Asymptomatic (not requiring escalating doses of steroids) brain metastases are acceptable.
    5. History of severe proteinuria (urine dipstick ≥ 2+ or 24 hr urine > 2gm/24hr)
    6. Prior history of hypertensive crisis or hypertensive encephalopathy
    7. History of a central nervous system disease (e.g. seizures) unrelated to cancer unless

adequately treated with standard medical therapy
8. Significant vascular disease (e.g. aortic aneurysm requiring surgical repair) ≤6 months prior to study enrollment
9. History of hemoptysis (≥1/2 teaspoon of bright red blood per episode) within the last 3 months
10. Evidence of a bleeding diathesis or significant coagulopathy (in the absence of therapeutic anticoagulation)
11. Current or recent (within 10 days of study drug start) use of aspirin (>325mg daily), clopidogrel (>75mg daily).
12. Recent initiation of full dose oral or parental anticoagulants that have not been in place for at least 2 weeks.
13. Tumor invading or abutting major blood vessels
14. Tumor histology classified by squamous cell histology.
15. Any history of abdominal fistula or GI perforation within 6 months of study enrollment

- Pregnant or lactating women
- Any type of systemic anticancer therapy (chemotherapy or experimental drugs) within 2 weeks of starting treatment on protocol.
- Any radiotherapy within 1 week of starting treatment on protocol.
- Any major surgery within 4 weeks of starting treatment on protocol.
- Any evidence of clinically significant interstitial lung disease
- Known hypersensitivity to any component of bevacizumab and osimertinib.

7.0 RECRUITMENT PLAN

A member of the patient's treatment team, the protocol investigator, or research team at Memorial Sloan Kettering Cancer Center will identify potential research participants. If the investigator is a part of the treatment team, s/he will screen the patient as to eligibility, and will discuss the study and the possibility of enrollment in the research study with the patient. The preliminary screen of eligibility will be confirmation for the diagnosis of the following:

- **Patients with metastatic EGFR mutant lung cancers**

Potential subjects that meet these basic criteria will be referred by their treatment physician to the investigator, co-investigators, or research staff of the study. Minority and women are well represented in the thoracic oncology clinics, and we expect that they will be well represented in the trial accrual. The principal investigator**, Dr. Helena Yu**, will be available to all patients for further questions and information through a contact number which will be provided on the consent form itself.

During the initial conversation between the investigator/research staff and the patient, the patient may be asked to provide certain health information that is necessary to the recruitment and enrollment process. The investigator/research staff may also review portions of their medical records at MSKCC in order to further assess eligibility. They will use the information provided by the patient and/or medical record to confirm that the patient is eligible and to contact the patient regarding study enrollment. If the patient turns out to be ineligible for the research study, the research staff will destroy all information collected on the patients during the initial conversation and medical records review, except for any information that must be maintained for screening log purposes.

All recruited patients will be under the care of attending medical oncologists of the MSKCC Thoracic Oncology Service. There will be no direct advertising for this study and participants will not be reimbursed for participation. Patients will be accrued to this study without regard for gender or minority status. The study will be available to the public and the details of the inclusion criteria, exclusion criteria and study design will be posted at www.clinicaltrials.gov.

8.1 PRETREATMENT EVALUATION

The following tests must be completed within 28 days of started treatment on study unless otherwise noted.

- Documented presence of the EGFR mutation within the patient's tumor (no time window)
- Medical history
- Baseline tumor assessment with CT scan of the chest/abdomen/pelvis is preferred, or other comparable radiologic study (PET scan) can be utilized if adequate assessment of target lesions can be performed. Tumor burden measurable by RECIST 1.1
- Baseline CNS assessment with contrast-enhanced MRI brain (or CT if MRI is contraindicated). This can be within 8 weeks of study start.
- Physical examination, vital signs (pulse, blood pressure, temperature, respiratory rate) as well as weight.
- 12-lead electrocardiogram (ECG) (within 8 weeks of study start)
- Performance status by KPS
- Serum or urine pregnancy test (for premenopausal women with child-bearing potential)
- Complete blood count with differential
- Comprehensive metabolic panel (glucose, blood urea nitrogen, creatinine, sodium, potassium, chloride, bicarbonate, calcium, total protein, albumin, serum bilirubin, alkaline phosphatase, ALT, AST)
- Urinalysis, dipstick
- EGFR T790M plasma blood test

9.1 TREATMENT/INTERVENTION PLAN

9.2 Therapeutic Agents

9.2.1 Therapeutic Agent – Osimertinib

Osimertinib will be provided by AstraZeneca. A pill diary will be used to track adherence. Osimertinib is administered daily, at approximately the same time of day every day. Osimertinib should be taken on an empty stomach (at least 1 hour before, or 2 hours after the ingestion of food). If the patient forgets to take his/her daily dose, he/she should take Osimertinib within 12 hours after the missed dose. If more than 12 hours have elapsed, that day's dose should be omitted, and the patients should continue treatment with the next scheduled dose.

9.2.2 Therapeutic Agent – Bevacizumab

Bevacizumab will be provided by Genentech. Bevacizumab is administered intravenously every 3 weeks (21 days) at the FDA approved dose level of 15 mg/kg. If an infusion is not tolerated well (ie.

Fever, chills) then the subsequent infusion(s) should be given over a prolonged infusion time (i.e. 60 – 90 min). Premedications (ie. Acetaminophen, diphenhydramine, corticosteroids) may be given to prevent/reduce the incidence/severity of reactions; however routine prophylactic use of premedications is not recommended.

9.2 Treatment arms

All patients will receive daily Osimertinib and every 3 week bevacizumab in this single-arm study.

9.3 Phase 1 study

This portion of the study will assess whether combination Osimertinib and bevacizumab is safe and tolerable. The study will follow a standard 3+3 dose escalation trial design. Three to six patients will need to be enrolled at each dose level and assessed for DLT for 1 full cycle (21 days). Toxicity will be graded according to NCI CTCAE version 4.0. Patients who do not complete 21 days of treatment for reasons other than experiencing a DLT will be replaced. For the purposes of dose-escalation decisions, only DLTs occurring during the first cycle (21 days) will be considered. Patients in each cohort must complete the first 3 weeks of study therapy prior to enrollment of subsequent cohorts.

9.4 Dose-Limiting Toxicities

The NCI Common Terminology Criteria for Adverse Events Version 4.0 (NCI-CTCAE) will be used to grade toxicities during the trial. Dose-limiting toxicities (DLT's) are defined as any of the following events occurring during the first cycle of treatment (i.e. 21 days) that are, in the opinion of the treating physician, possibly, probably, or definitely related to the investigational regimen:

- Death related to the investigational regimen
- Hematologic toxicities including:
    - Grade 4 neutropenia lasting > 5 days
    - Grade 4 thrombocytopenia (<25,000/mm^3)
    - Grade ≥ 3 thrombocytopenia with evidence of clinically significant bleeding
    - Grade 4 anemia
- Non-hematologic toxicities including:
    - Grade ≥ 3 AST, ALT, alkaline phosphatase or total bilirubin
    - Grade ≥ 3 diarrhea, nausea, vomiting that lasts > 72 hrs despite optimal maximal supportive care
    - Grade ≥3 rash that persists >7 days despite supportive medications
    - Grade ≥4 diarrhea, nausea or vomiting
    - Any other non-hematologic grade ≥ 3 major organ toxicity

9.5 Phase 2 Study

Once the phase 1 portion of the study has been completed, patients will be enrolled in the phase 2 portion of the single-arm study of Osimertinib and bevacizumab in the treatment of patients with EGFR-mutant lung cancers. Response to therapy will be assessed by interval imaging every 9 weeks +/- 1 week (every 3 cycles) with CT scan of the chest/abdomen/pelvis with response evaluated by RECIST 1.1. A maximum of 46 patients will be enrolled during this portion of the study. This phase 2 total accrual will include six patients treated at the MTD in the phase 1. To reach the primary endpoint of the phase 2 study, 43 patients will need to be response evaluable. As a result, a

total of 46 patients will be enrolled to account for potential patient-drop out.

9.6 Correlative Studies

Molecular testing will be performed on archived pre-treatment tumor specimens if available. A rebiopsy at the time of clinical progression on EGFR TKI will not be mandated per protocol, but is typically done as per standard of care.

EGFR T790M is routinely identified in tumor tissue by several standard methods including a mass spectrometry based mutation platform (Sequenom), locked nucleic acid based PCR sequencing or by next generation sequencing. Our next-generation sequencing based mutation platform (IMPACT) will be performed to compare the molecular alterations in pre and post treatment specimens. The sequencing data will be analyzed for base mutations, insertions, deletions, copy number alterations and genomic rearrangements in all target genes.

9.6.1 Optional Studies

We propose to an obtain biopsy in patients with metastatic EGFR-mutant lung cancer at initial clinical response at 4 weeks +/- 1 week on study. There will be an optional CT scan at 4 weeks to demonstrate response, and an optional biopsy of residual disease in patients without disease progression on that initial scan. Patients that provide consent to the optional 4 week scan and biopsy will allow us to better understand the molecular mechanisms underlying intrinsic and acquired resistance. We will be performing IMPACT testing on these obtained samples, and compare to the pre-treatment and post-treatment tumor samples.

9.7 **Treatment Beyond Disease Progression**

Subjects will be permitted to continue study treatment beyond initial RECIST 1.1 defined PD, assessed by the investigator, as long as they meet the following criteria:

- Investigator-assessed clinical benefit, and do not have rapid disease progression
- Tolerance of study drug
- Stable performance status
- Subject provides written informed consent prior to receiving additional study treatment acknowledging the possibility of any reasonably foreseeable risk or discomforts, as well as the possibility of alternative treatment options.

The assessment of clinical benefit should take into account whether the subject is clinically deteriorating and unlikely to receive further benefit from continued treatment.

If the investigator feels that the subject continues to achieve clinical benefit by continuing treatment, the subject should remain on the trial and continue to receive monitoring according to the Study Calendar in Section 10.0. A radiographic assessment should be performed at the next scheduled time point to determine whether there has been a decrease in the tumor size or continued progression of disease.

10.0 EVALUATION DURING TREATMENT/INTERVENTION

The table below outlines the schedule of assessments applied to patients. All assessments, including drug dosing, have a window of +/- 5 days for cycle 1, and +/- 7 days for cycle 2 and beyond unless otherwise noted. If the subject is unable to have a study assessment taken within the defined time window due to an event outside of his or her control (e.g. clinic closure, personal emergency, inclement weather, vacation) the assessment should be performed as close as possible to the required schedule, at which time the window clock will reset and the patient will have a +/- 7 day window from the date of their visit. Tumor assessments have a window of +/- 1 weeks. If an appropriate imaging study is done for an unrelated reason, it can be used for disease assessment if it falls within the appropriate time frame. Subjects will return to the study site within 30 days after their last dose of Osimertinib and bevacizumab to complete end of study assessments outlined below.

Study Assessments	**Screening**	**Cycle 1**		**Cycle 2+**	**At Progression/Off Study**
Day	Within 4 weeks	C1D1	C1D8	C2D1 +	
Informed Consent	X				
Medical History	X	X	X	X	X
Physical Exam	X	X	X	X	X
Vital Signs	X	X	X	X	X
Adverse Events		X	X	X	X
12-lead EKG	X				
Tumor Assessment[1, 8]	X			X	X
Pregnancy Test[6]	X			X[6]	
CBC[2]	X	X		X	X
CMP[3]	X	X		X	X
Urinalysis, Dipstick[5,10]	X			X	

IMPACT testing[4]	X	X	
EGFR T790M testing[7]	X		X[7]
Tumor Biopsy[9] (optional)		X[9]	X[9]

1. CT chest/abdomen/pelvis with or without contrast (preferred and will be used for all subsequent scans after screening). CT will be done at screening, every 9 weeks (+/- 1 week) and at progression, or when patient comes off study. An MRI of the brain, or a comparable study, will be done every 18 weeks (+/- 1 weeks), unless patient is found to have brain metastases after baseline/FU 1 scans are completed. If brain metastases are found, the patient will have a brain MRI completed every 9 weeks instead of every 18 weeks. Patients that do not have brain metastases will still require a brain MRI every 18 weeks on study.
2. CBC- complete blood count with differential
3. CMP-comprehensive metabolic panel (glucose, blood urea nitrogen, creatinine, sodium, potassium, chloride, bicarbonate, calcium, total protein, albumin, serum bilirubin, alkaline phosphatase, ALT, AST)
4. IMPACT molecular profiling will be done on pre-treatment archived tissue if available. If a post-progression biopsyis performed as standard of care, IMPACT molecular results will be obtained. A post-progression biopsyis not mandatoryor included in the protocol.
5. Urinalysis, dipstick will be done at screening and every 2 cycles to monitor for proteinuria. If urine protein (dipstick) is > 2+, then a 24 hour urine protein test will be administered.
6. A urine pregnancy test will be done every 4 cycles for women of childbearing age.
7. An EGFR T790M plasma blood test is to be completed at screening and at progression or off study.
8. Optional tumor assessment scans will be completed 4 weeks post Cycle 1 Day 1 (+/- 14 day window) to determine initial clinical response.
9. Optional tumor biopsywill be completed within 2 weeks (=/- 14 day window) post the optional 4 week tumor scan if initial clinical response is confirmed. Patient must consent to both optional assessments. Initial clinical response is defined as stable disease, a partial response or a complete response to treatment.
10. Urinalysis, dipstick is not required for patients who have discontinued bevacizumab.

11.0 TOXICITIES/SIDE EFFECTS

Adverse events occurring in patients treated with Osimertinib and bevacizumab may be 1) overlapping toxicities seen in both agents; 2) toxicities typically associated with Osimertinib (i.e. rash, diarrhea) or 3) toxicities typically associated with bevacizumab (hypertension). However, toxicities with individual agents may be potentiated in the combination or unanticipated AEs may occur. The dose modifications or discontinuations may involve one or both agents, and should be based on the nature, severity, and attributions of the AEs. Differentiation of the causative agent for adverse events for the purposes of dose modifications are at the discretion of the treating physician and/or principal investigator. General guidelines are provided below.. For safety and adverse event reporting, see **Section 17.0.**

While AEs may be thought to be related to individual agents for purposes of dose modifications, all toxicities will be considered related to combination therapy for description of AE profile.

11.1 **Osimertinib Related Toxicities:**

Toxicities with Osimertinib that are likely (>20%) include:

- Rash
- Diarrhea
- Nausea
- Decreased appetite
- Dry skin

Toxicities with Osimertinib that are less likely (<20%) include:

- Itchy skin
- Decreased energy
- Nail changes
- Mucositis
- Constipation
- Cough
- Vomiting
- Low red blood cell counts which can lead to fatigue
- Shortness of breath
- Upper respiratory tract infections
- Headache

Side effects of Osimertinib that are rare, but serious include:

- Pneumonitis (inflammation of the lung). Fatal events of inflammation of lungs have been reported in patients taking Osimertinib.

11.1 **Bevacizumab Related Toxicities:**

Toxicities with Bevacizumab that are likely (>20%) include:

- Mild to moderate increase in blood pressure
- Protein in urine, which rarely leads to damage to the kidney
- Shortness of breath
- Nosebleeds
- Headache
- Loss of appetite
- Sore mouth or throat
- Constipation
- Feeling tired
- Diarrhea
- Nausea and vomiting
- Generalized pain and pain in the abdomen (belly)
- Heartburn

Toxicities with Bevacizumab that are less likely (<20%) include:

- Mild to moderate decrease in blood pressure
- Blood clots in veins or arteries, which may be life threatening
- Mild to moderate bleeding in the tumor, stomach, intestines, vagina or lungs

- Reactions associated with bevacizumab infusion: chills, fever, rigors
- Rash, skin ulcer, hives, welts or itching
- Infection
- Dizziness
- Pains in the muscles and joints
- Chest pain
- Cough
- Nasal stuffiness, sneezing, post nasal drip
- Wheezing
- Weight loss
- Voice changes, hoarseness, laryngitis
- Damage to the heart muscle resulting in decrease in heart function
- Low white blood cell counts, which may make you more at risk for infection.

Side effects of Bevacizumab that are rare, but serious include:

- Problems with wound healing
- Development of an abnormal opening (fistula) between the large intestine (bowel) and another organ, most commonly the bladder, uterus or vagina
- Bowel perforation. This can occur when an opening forms in the bowel wall allowing bowel contents to spill into the abdomen. This is rare but often requires surgery and can be life-threatening and fatal.
- Bowel anastomotic dehiscence: This is a breakdown in the surgical connection between two pieces of bowel in patients with prior history of bowel surgery. This is rare but often requires surgery and can be life-threatening and fatal
- Severe allergic reactions that result in difficulty breathing or drop in blood pressure
- Serious or fatal bleeding from the tumor, brain, gut or lungs
- Heart problems, including irregular heartbeats, heart attack or heart failure
- Reversible changes in the liver function
- Nephrotic syndrome, a type of kidney disease caused by damage to the tiny blood vessels in the kidney
- Reversible Posterior Leukoencephalopathy Syndrome (RPLS) or similar leukoencephalopathy syndrome. RPLS is a medical condition related to leakiness of blood vessels in the brain. This can cause confusion, blindness or vision changes, seizure and other symptoms. This condition is usually reversible. In rare cases it can be life threatening and may have a long term effect on brain function.

11.2 Dose modifications will not be allowed for cycle 1 during the Phase 1 portion of the protocol in order to ensure accurate assessment of the MTD. General guidelines are below:

Osimertinib Dose modifications (Cycle ≥2 only)

Dose at time of toxicity	Dose reduction levels
80mg	40mg
40mg	40mg every other day

If a patient experiences a CTCAE grade 3 or higher and/or unacceptable toxicity (any grade), where the Investigator considers the AE to be associated with the study drug, dosing will be interrupted and

supportive therapy administered as required in accordance with local practice/guidelines. If the AE is clearly attributable to one drug and not the other, only the culprit drug will be held. If an AE is not clearly attributable to one drug, both drugs will be held until the AE resolves as specified below.

If the toxicity resolves or reverts to ≤CTCAE grade 1 within 2 weeks of onset, study drug may be restarted at the same dose (starting dose) or reduced dose using the dose reduction in the table above. If restarting at the same dose level, patients should be closely monitored for 3 days following the restart of treatment. If within 3 days there is recurrence of same toxicity, a dose reduction should be considered at the Investigator's discretion.

If the toxicity does not resolve to ≤CTCAE grade 1 after 2 weeks, then the patient should be withdrawn from the study treatment and observed until resolution of the toxicity. Resumption of the study drug at a lower dose would require discussion with the sponsor and Principal Investigator. If one drug is permanently discontinued, it is the treating physician's discretion as to whether to continue the other drug as monotherapy.

Patients who develop asymptomatic Gr. 3 or Gr. 4 lymphopenia without clinical correlate (eg. Opportunistic infection) may continue study treatment without interruption if approved by the treating physician.

For any toxicity, supportive medications should be utilized. For example, for skin reactions, mild to moderate strength steroids creams, either topical or systemic antibiotics should be started, as seen appropriate by the investigator upon assessment of the skin reaction. For nausea/vomiting, anti-emetic therapy should be utilized. For diarrhea, after alternative etiologies are ruled out, anti-diarrheal medications should be utilized.

QTC prolongation: For patients with ≥CTCAE grade 3 QTC prolongation should have study drug interrupted and monitoring of ECGs performed until resolution to baseline. If the toxicity resolves or reverts to ≤CTCAE grade 1 within 2 weeks of onset, study drug may be restarted at the same dose or reduced dose using the dose reduction levels in the table above. If the toxicity does not resolve to ≤CTCAE grade 1 within 2 weeks, the patient will be permanently withdrawn from study drug.

Interstitial lung disease/pneumonitis:
If a new or worsening of pulmonary symptoms (e.g., dyspnea) or occurrence of a radiological abnormality suggestive of ILD is observed, an interruption in study drug dosing is recommended. In the presence of confirmatory CT scans where other causes of respiratory symptoms have been excluded, a diagnosis of ILD should be considered and study drug permanently discontinued. In the absence of a diagnosis of ILD, study drug may be restarted following consultation with the Principal investigator and sponsor.

Please refer to the package insert for further details.

Bevacizumab

Bevacizumab dose will not be reduced for reasons other than a >10% change in weight from baseline. Bevacizumab treatment may be either temporarily or permanently suspended in the case of bevacizumab-related events such as fistulae, GI perforation, hypertension, proteinuria, thrombosis/embolism, hemorrhage, CHF, wound healing complications, PRES (or RPLS) and hypersensitivity/allergic reactions in addition to any other serious bevacizumab-related toxicity (grade 3 or 4).

In addition, bevacizumab should be temporarily withheld in the event of febrile grade 4 neutropenia and/or grade 4 thrombocytopenia (regardless of the relationship to treatment), since these conditions are predisposing factors for an increased bleeding tendency. To summarize, bevacizumab should be held temporarily or permanently discontinued in patients (as per the clinical judgment of the treating physician) experiencing any of the following events:

- Febrile grade 4 neutropenia and/or grade 4 thrombocytopenia regardless of the relationship to treatment (hold treatment temporarily)
- Grade ≥ 2 fistula (hold temporarily or permanently discontinue)
- GI perforation (permanently discontinue)
- Major surgery or wound healing complications (hold temporarily or permanently discontinue)
- Medically significant hypertension not controlled with antihypertensive therapy, hypertensive crisis or hypertensive encephalopathy (permanently discontinue)
- Grade ≥ 3 left ventricular dysfunction (CHF) (permanently discontinue)
- Nephrotic syndrome (permanently discontinue)
- Arterial thrombosis/embolism (any grade) (permanently discontinue)
- Grade ≥ 3 venous thrombosis/embolism (hold temporarily or permanently discontinue for grade 4)
- CNS bleeding (any grade) or ≥ grade 3 bleeding of any kind (permanently discontinue)
- Grade ≥ 2 hemoptysis (hold temporarily or permanently discontinue)
- Hypersensitivity/allergic reactions related to bevacizumab (permanently discontinue)
- PRES (or RPLS) (permanently discontinue)

If bevacizumab is permanently suspended, patients will no longer need to have Urinalysis, Dipstick done every 2 cycles to measure proteinuria.

Posterior Reversible Encephalopathy Syndrome (PRES/RPLS)

There have been rare reports of patients treated with bevacizumab developing signs and symptoms that are consistent with PRES, a rare neurological disorder. PRES is also known as reversible posterior leukoencephalopathy syndrome or RPLS). PRES can present with following signs and symptoms among others: seizures, headache, altered mental status, visual disturbance or cortical blindness, with or without associated hypertension. A diagnosis of PRES requires confirmation by brain imaging. In patients developing PRES, treatment of specific symptoms including control of

hypertension is recommended along with discontinuation of bevacizumab. The safety of reinitiating bevacizumab therapy in patients previously experiencing PRES is not known. Adequate brain imaging using MRI must be performed as a follow-up measurement for patients with PRES.

Gastrointestinal Perforation and Fistula

Bevacizumab has been associated with serious cases of GI perforation in patients with mCRC and a few reports of gallbladder perforation have been reported from the post-marketing experience. The presentation of these events has varied in type and severity, ranging from free air seen only on the plain abdominal X-ray, which resolved without treatment, to a colonic perforation with abdominal abscess and fatal outcome. The common feature among these cases was intra abdominal inflammation, either from gastric ulcer disease, tumor necrosis, diverticulitis or chemotherapy-associated colitis. Nevertheless, a causal association of an intra-abdominal inflammatory process and GI perforation to treatment with bevacizumab has not been established. However, caution should be exercised when treating patients with intra-abdominal inflammatory process with bevacizumab. Bevacizumab should be permanently discontinued in patients who develop GI perforation.
Bevacizumab use has been associated with serious cases of fistulae including events resulting in death. Fistulae within the GI tract or GI tract and skin are common in patients with mCRC and ovarian cancer, but are uncommon or rare in other indications. Other fistulae (e.g. tracheoesophageal, bronchopleural, urogenital, biliary) have been reported uncommonly in bevacizumab clinical trials patients and in post-marketing reports. Temporarily discontinue bevacizumab in patients with grade 2 or 3 non- tracheoesophageal fistula until resolution to ≤ grade 1. Permanently discontinue bevacizumab in patients with tracheoesophageal fistula or any grade 4 fistula. Limited information is available on the continued use of bevacizumab in patients with other fistulae. In cases of internal fistula not arising in the GI tract, discontinuation of bevacizumab should be considered.

Wound Healing Complications

Increased incidences of post-operative bleeding or wound healing complications have been observed in clinical trials of bevacizumab in relapsed glioma and mCRC and BC. Bevacizumab therapy should not be initiated for at least 28 days following major surgery or until the surgical wound is fully healed as bevacizumab may adversely impact wound healing. In patients who experience wound healing complications during bevacizumab treatment, bevacizumab should be withheld until the wound is fully healed. If the wound does not fully heal despite withholding treatment, should be permanently discontinued.
Bevacizumab therapy should be withheld for an interval of at least two half-lives (approximately six weeks) before conducting major elective surgery. Emergency surgery should be performed as appropriate without delay after a careful risk-benefit assessment.

Hypertension

An increased incidence of hypertension has been observed in patients treated with bevacizumab. Clinical safety data suggest the incidence of hypertension is likely to be dose-dependent. Pre-existing hypertension should be adequately controlled before starting bevacizumab treatment. There is no information on the effect of bevacizumab in patients with uncontrolled hypertension at the time of initiating therapy. Blood pressure must be assessed before each bevacizumab administration. In most cases hypertension is controlled adequately using standard antihypertensive treatment

appropriate for the individual situation of the affected patient. Bevacizumab should be permanently discontinued if medically significant hypertension cannot be adequately controlled with antihypertensive therapy, or if the patient develops hypertensive crisis or hypertensive encephalopathy.

Congestive Heart Failure (CHF)

Events consistent with CHF were reported in clinical trials. The findings ranged from asymptomatic declines in left ventricular ejection fraction (LVEF) to symptomatic CHF, requiring treatment or hospitalization. Most of the patients who experienced CHF had metastatic breast cancer and had received previous treatment with anthracyclines, prior radiotherapy to the left chest wall or other risk factors for CHF were present. Caution should be exercised when treating patients with clinically significant cardiovascular disease such as pre-existing coronary artery disease, concomitant cardiotoxic therapy or CHF with bevacizumab. Bevacizumab should be permanently discontinued in patients with ≥ grade 3 CHF.

Proteinuria

In clinical studies, the incidence of proteinuria was higher in patients receiving bevacizumab in combination with chemotherapy compared to those who received chemotherapy alone. Proteinuria reported as an AE with bevacizumab treatment has ranged in severity from clinically asymptomatic, transient, trace proteinuria to nephrotic syndrome with the great majority as grade 1 proteinuria. The proteinuria seen in bevacizumab clinical trials was not associated with renal dysfunction and rarely required permanent discontinuation of bevacizumab therapy. Patients with a history of hypertension may be at increased risk for the development of proteinuria when treated with bevacizumab. Proteinuria must be assessed by dipstick before each bevacizumab administration unless proteinuria has been determined by 24-hour urine collection. Patients who have permanently discontinued bevacizumab will not be tested for proteinuria with dipstick.

Table 11.1 Bevacizumab Treatment Management for Proteinuria

NCI CTCAE v. 4.0	Urinalysis	Treatment Action
Grade 1	1+ proteinuria urinary protein < 1.0 g/24 hrs	No bevacizumab dose modification
Grade 2	2+ proteinuria urinary protein 1.0-3.4 g/24 hrs	For 2+ dipstick: may administer bevacizumab without dose modification and collect 24-hour urine prior to subsequent bevacizumab administration. For 3+ dipstick: must obtain 24-hour urine prior to administering bevacizumab Suspend bevacizumab for urinary protein ≥2 g/24 hrs. Resume bevacizumab when proteinuria is < 2 g/24 hrs.
Grade 3	urinary protein ≥3.5 g/24 hrs	Suspend bevacizumab. Resume bevacizumab when proteinuria is < 2 g/24 hrs.
Nephrotic syndrome		Permanently discontinue bevacizumab

Arterial thrombosis/embolism

Bevacizumab should be discontinued in patients who develop arterial thromboembolic events. A history of arterial thromboembolic events or age greater than 65 years has been associated with an increased risk of arterial thromboembolic events during bevacizumab therapy. Patients receiving bevacizumab plus chemotherapy with a history of arterial thromboembolism and age greater than 65 years have a higher risk. Caution should be taken when treating these patients with bevacizumab.

Venous thrombosis/embolism

Bevacizumab should be held in patients developing a grade 3 thrombosis/embolism. Bevacizumab may be resumed once the patient is adequately anti-coagulated and on a stable level of anticoagulation for at least 2 weeks prior to restarting study drug treatment. Patients on heparin treatment should have an aPTT between 1.5-2.5 x ULN (or patient value before starting heparin treatment). Patients on coumarin derivatives should have an INR between 2.0 and 3.0 assessed in two consecutive measurements 1-4 days apart. Patients on full dose low molecular weight heparins should receive the appropriate dose based on the weight of the patient according to package insert. An increased risk of venous thromboembolic events and bleeding in patients receiving anti-coagulation therapy after first venous thromboembolic event while receiving bevacizumab has been observed. In the event of recurrent grade 3 thrombosis/embolism, the patient should be discontinued from bevacizumab. Bevacizumab should be discontinued in patients with life-threatening (grade 4) pulmonary embolism.

Hemorrhage

An increased incidence of bleeding events was observed in study patients treated with bevacizumab as compared to control treatment arms. The hemorrhagic events observed in bevacizumab studies were predominantly tumor-associated hemorrhage and minor mucocutaneous hemorrhage. Patients with untreated CNS metastases were routinely excluded from clinical trials with bevacizumab, based on imaging procedures or signs and symptoms. Therefore, the risk of CNS hemorrhage in such patient has not been prospectively evaluated in randomized clinical studies. Bevacizumab should be permanently discontinued for:

- grade 3 or 4 bleeding of any kind
- any grade of CNS bleeding. Patients should be monitored for signs and symptoms of CNS bleeding.

Bevacizumab should be temporarily held or permanently discontinued for grade ≥ haemoptysis (defined as ≥ 2.5 mL bright red blood per episode). The safety of re-initiating bevacizumab in patient's previously experiencing grade ≥ 2 haemoptysis has not been evaluated. If hemorrhagic complications occur in patients on full dose anti-coagulation therapy, permanently discontinue bevacizumab treatment and follow guidelines of the treating institution. Standard procedures such as antagonisation with protamin or vitamin K and infusion of vitamin K dependent factors should be considered dependent on the severity of the bleeding.

Hypersensitivity/Allergic Reactions and Infusion-Associated Reactions

Bevacizumab should be permanently discontinued in patients exhibiting hypersensitivity/allergic reactions. The NCI CTCAE distinguish between hypersensitivity reactions and acute infusion reactions induced by cytokine release. Despite the different possible mechanisms underlying hypersensitivity and infusion reactions, the clinical signs and symptoms associated with these reactions overlap. Patients may be at risk of developing infusion reactions to bevacizumab. Close observation of the patient during and following the administration of bevacizumab is recommended as expected for any infusion of a therapeutic humanised monoclonal antibody. If an infusion reaction occurs, the infusion should be discontinued and appropriate medical therapies should be administered. A systematic premedication is not warranted.

Osteonecrosis of the Jaw

Osteonecrosis of the jaw was reported in patients receiving bevacizumab mainly in combination with bisphosphonates in the post-marketing setting. The pathogenesis of the osteonecrosis is unclear. For further information, please refer to the Avastin® Investigator' Brochure.

Ovarian Failure

Ovarian failure has been reported more frequently in patients receiving bevacizumab. Ovarian function recovered in the majority of women after bevacizumab discontinuation. For further information, please refer to the Avastin® Investigator' Brochure.

Bevacizumab experience in lung cancer trials:

Of patients experiencing pulmonary hemorrhages requiring medical intervention, many had cavitation and/or necrosis of the tumor, either preexisting or developing during bevacizumab therapy. Patients developing lung cavitation on treatment should be assessed by the treating physician for

risk-benefit. In Study E4599, in which squamous cell carcinoma was excluded, the rate of any type of Grade ≥ 3 hemorrhage was 1.0% in the control arm (carboplatin and paclitaxel) versus 4.1% in the carboplatin and paclitaxel + bevacizumab arm (Sandler et al. 2006). GI hemorrhages, including rectal bleeding and melena have been reported in patients with CRC, and have been assessed as tumor-associated hemorrhages. Tumor-associated hemorrhages were also seen rarely in other tumor types and locations and included cases of CNS bleeding in patients with CNS metastases and in patients with glioblastoma.

The incidence of CNS bleeding in patients with untreated CNS metastases receiving bevacizumab has not been prospectively evaluated in randomised clinical studies. In an exploratory retrospective analysis of data from 13 completed randomised trials in patients with various tumor types, 3 patients out of 91 (3.3%) with brain metastases experienced CNS bleeding (all Grade 4) when treated with bevacizumab, compared to 1 case (Grade 5) out of 96 patients (1%) that were not exposed to bevacizumab. In two subsequent studies in patients with treated brain metastases (which included around 800 patients), one case of Grade 2 CNS haemorrhage was reported. Intracranial haemorrhage can occur in patients with relapsed glioblastoma. In study AVF3708g, CNS haemorrhage was reported in 2.4% (2/84) of patients in the Avastin alone arm (Grade 1); and in 3.8% (3/79) of patients treated with Avastin and irinotecan (Grades 1, 2 and 4). Patients with untreated CNS metastases were routinely excluded from clinical trials with Avastin, based on imaging procedures or signs and symptoms. Therefore, the risk of CNS haemorrhage in such patient has not been prospectively evaluated in randomised clinical studies. Patients should be monitored for signs and symptoms of CNS bleeding, and Avastin treatment discontinued in cases of intracranial bleeding.

12.0 CRITERIA FOR THERAPEUTIC RESPONSE/OUTCOME ASSESSMENT

The same method of assessment and the same technique (i.e. with or without contrast) should be used to characterize each identified and reported lesion at baseline, and every nine weeks (+/- 1 weeks). Designated radiologists at MSKCC (named on the study face sheet) will interpret the study CTs according to RECIST 1.1 criteria.

Tumor response will be assessed using RECIST 1.1. A CT chest/abdomen/pelvis will be performed to demonstrate all known areas of measurable disease. The baseline study will occur no more than 4 weeks prior to first study drug administration. A CT scan with contrast will be the preferred method and modality of imaging. A CT scan without contrast can be used in patients with contraindications to radiographic contrast media used in CT scans. All patients must have at least one measurable disease lesion by CT. MRI brains (+/- spine) will be required as well to assess CNS involvement.

All measurable lesions, up to a maximum of 5 lesions total, representative of all involved organs should be identified as target lesions and recorded and measured at baseline. Target lesions should be selected on the basis of their size, should be representative of all involved organs, and should lend themselves to reproducible repeat measurements. All other lesions (or sites of disease) should be identified as non-target lesions and should also be recorded at baseline as well. Definitions of response in target and non-target lesions are described in Table 12.1 and 12.3 below. Table 12.3 provides overall responses for all possible combinations of tumor responses in target and nontarget lesions.

Table 12.1: Evaluation of target lesions	
Complete Response (CR):	Disappearance of all target lesions
Partial response (PR)	At least a 30% decrease in the sum of the diameters of the target lesions
Progressive disease (PD):	At least a 20% increase in the sum of the diameter of the target lesions or the appearance of one or more new lesions
Stable disease (SD):	Neither sufficient shrinkage to qualify for PR nor sufficient increase to qualify for PD

Table 12.2: Evaluation of non-target lesions	
Complete Response (CR):	Disappearance of all non-target lesions
Incomplete response/Stable disease (SD):	Persistence of one or more non-target lesions
Progressive disease (PD):	Appearance of one or more new lesion and/or unequivocal progression of existing non-target lesion

Table 12.3: Combinations of responses			
Target lesions	**Nontarget lesions**	**New lesions**	**Overall response**
CR	CR	No	CR
CR	Incomplete/SD	No	PR
PR	Non-PD	No	PR
SD	Non-PD	No	SD
PD	Any	Yes or No	PD
Any	PD	Yes or No	PD
Any	Any	Yes	PD

Discontinuation of treatment

Early death is defined as having no repeat tumor assessments following initiation of study therapy resulting from death of the patient due to disease or treatment. Patients with global deterioration of health status requiring discontinuation of treatment without objective evidence of disease progression will be recorded as 'symptomatic deterioration'. Every effort will be made to document objective progression even after discontinuation of treatment.

Evaluation of best overall response

The best overall response is the best response recorded from the start of treatment until disease progression, as defined in Table 12.3.

Other definitions

Evaluable for toxicity: All patients who receive ≥ 80% of all treatment doses with osimertinib and bevacizumab during cycle 1 of phase I will be evaluable for toxicity during the DLT period. However, patients who are replaced during the first cycle of treatment in the dose de-escalation phase for any reason other than DLT will not be included in the assessment of MTD.

Evaluable for efficacy: All patients at MTD will be included in the analysis of efficacy. Patients

treated at the MTD with a DLT who do not continue treatment on study will not be included in the phase 2 portion of the study. If patients at the MTD with a DLT continue on study, they will be included in the efficacy analyses.

Progression-free survival (PFS) is defined as the duration of time from first treatment to time of progression (in the CNS or systemically) or death, whichever occurs first.

Intracranial progression-free survival (PFS) is defined as the duration of time from first treatment to time of progression (in the CNS) or death, whichever occurs first.

Overall survival (OS) is defined as the duration of time from first treatment to time of death.

13.0 CRITERIAFOR REMOVAL FROM STUDY

Patients may withdraw from the study at any time. Other reasons for study discontinuation include but are not limited to:

- Change in patient eligibility
- Non-compliance with the defined treatment plan
- Protocol violation
- Investigator's decision based on patient's best interest
- W ithdrawal of consent
- Severe, unexpected toxicities/side effects
- Lost to follow up
- Death
- Progression of disease (defined by RECIST 1.1)

For the Phase 1 portion of the study, patients who withdraw from the study for reasons other than DLT without completing a full treatment cycle will be replaced.

14.0 BIOSTATISTICS

Phase 1:

Primary Objective: To determine the safety and tolerability of the combination of osimertinib and bevacizumab in patients with EGFR mutant lung cancers.

Endpoints: Identify any dose limiting toxicities of the combination and establish the MTD. A dose limiting toxicity is a binary outcome where a patient either experiences a DLT or not. DLT is defined as any of the toxicities described in Section 9.4 that occurs within one cycle after initiation of treatment with osimertinib and bevacizumab. The MTD is defined as the highest dose at which not more than 1/6 of the patients experience a DLT.

Method: A standard 3+3 design will be used to find the maximum tolerated dose (MTD). We will begin with dose level 1 and de-escalate to dose level -1 if significant toxicity is seen with the combination.

Table 14: Dose levels

Dose level	Osimertinib	Bevacizumab
-1	40mg daily	15mg/kg every 3 weeks
1	80mg daily	15mg/kg every 3 weeks

Three patients will be enrolled at dose level 1 (Osimertinib 80mg once daily and bevacizumab 15mg/kg intravenously once every three weeks and assessed for dose limiting toxicities (DLTs) for 1 full cycle (21 days). Toxicity will be graded according to NCI CTCAE version 4.0.

If 0-1 DLTs occur at dose level 1 during cycle 1, an additional 3 patients will be treated at dose level 1. If 0-1 DLTs occur during cycle 1 in the 6 patients treated, dose level 1 will be determined to be the MTD. If 2 or greater DLTs occur at dose level 1, we will de-escalate to dose level -1.

The dose escalation scheme is as follows:

1. If zero to one of the initial three patients at a given dose level experiences DLT, three additional patients will be treated at the same dose level.
2. If two or more patients experience DLT at dose level 1, 3 patients will be treated at dose level -1.
3. Should two or more patients experience the DLT at dose level -1, the study will be halted, and alternative combination dosing will be considered.
4. If only three patients were treated at a dose under consideration as the MTD, an additional three patients will be treated at that level to confirm previous results.

Thus, the maximum number of patients that will be enrolled in the phase I portion is 12 (6 at each dose level). The probability of escalation given different true rates of dose-limiting toxicity is given below

Toxicity rate	0.10	0.20	0.30	0.40	0.50
Probability of escalation	91%	71%	49%	31%	17%

The MTD will be the recommended dose for the phase 2 portion. At the completion of the phase 1 portion, 6 patients will have been treated at the MTD. These patients will be followed for response assessment and included in the phase 2 portion of the study. Patients treated at the MTD with a DLT who do not continue treatment on study will not be included in the phase 2 portion of the study. If patients at the MTD with a DLT continue on study, they will be included in the efficacy analyses. Given an expected accrual rate of 2 patients per month, the phase 1 portion of the study will be completed within 6 months or less.

Phase 2:

Primary Objective: Assess the progression-free survival at 12 months of combination Osimertinib and bevacizumab in patients with untreated EGFR-mutant lung cancers.

Secondary Objective: 1) Measure overall response rate (CR+PR), 2) measure progression-free survival 3)measure intracranial progression-free survival 4) measure overall survival 5) further define the toxicity profile of the combination

Methods:

A thirty patient subgroup of the AURA study received Osimertinib 80mg daily as first-line treatment for EGFR-mutant lung cancer (Ram lingam PASCO 2015). After 12 months of follow up, the median PFS was not yet reached. The percent of progression-free surviving patients is 73% at 12 months with a 95% CI of 51% to 87%. We decided to use the lower bound of the 95% CI of 1-year PFS from the AURA study with 51% as the historical control.

Hoping to see an improvement in 1-year PFS from 51% to 70%, we will need 43 patients to provide 80% power while controlling the Type I error at 5% in a single-stage design. We will need to see at least 28 patients alive and free from progression at 12 months in order to consider this treatment strategy promising. Overall survival (OS), progression-free survival at 12 months and progression-free survival (PFS) will be estimated using the Kaplan-Meier method, with the follow-up starting at the initiation of therapy. Patients will be censored at the time of the last on-study evaluation if they do not experience the event of interest. Intracranial progression will be calculated by looking specifically for growth or new lesions or leptomeningeal disease in the central nervous system. Overall response rate (CR + PR) will be calculated, utilizing best overall response, including exact 95% confidence intervals.

Patients who undergo intra-patient dose escalation from dose -1 to dose 1 if dose 1 is established as the MTD, will not be included in the response rates, PFS, or OS. Safety and tolerability will be summarized using descriptive statistics. The toxicities and the adverse events will be assessed for each patient according to the NCI CTCAE version 4.0 criteria. Given an expected accrual rate of 2 patients per month, the accrual for the expansion portion of the study will be completed in about 19 months. If an efficacy signal is seen when assessing the PFS at one year, a larger, multicenter, randomized study will be considered to more accurately compare the efficacy of Osimertinib monotherapy to Osimertinib plus bevacizumab.

Patients will remain on study until progression or they come off study treatment for other reasons. Patients will have an end of treatment visits that concludes study follow up. They will not be contact directly once off study treatment, but every effort with be made to document their disease progression and survival status for the progression-free survival rate at 12 months and overall survival information. If patients' disease progression status is unobserved at 12 months despite the effort, they will be counted as progression so that the PF survival rate at 12 months will be a conservative estimate.

Correlative Studies:

Primary Objective: 1) to identify EGFR T790M in pre and post treatment samples 2) perform next-generation sequencing based mutation testing on tumors before treatment and at progression.

Correlatives: For the correlative studies, the analysis is primarily exploratory and hypothesis generating. Correlative studies will be performed on all patients, (from the phase 1 and 2 portions of the study) including descriptive summaries of mutation testing. The only exception is the IMPACT analyses which will be limited to patients with samples available. There is an optional tumor biopsy at best response.Tissue will only be available after protocol treatment from subjects who agree to a standard of care post-progression biopsy. While all the genes in the IMPACT panel will be assessed, only those with at least 10% prevalence in this trial will be statistically analyzed.

Method:
EGFR T90M status will be determined pre-treatment for all patients and post treatment in those patients who progress using direct sequencing. The proportion of patients with T790M mutation in both tumor tissue will be calculated along with the exact 95% confidence interval. The pre- treatment EGFR T790M mutations along with the gene mutations identified by the IMPACT panel will be univariately correlated with response using Chi-squared test and with PFS and OS using logrank test. Since the expected number of genes to be analyzed is in the order of hundreds, the Benjamini-Hochberg procedure (15) will be considered to control the false discovery rate at 0.05 level.

15.1 RESEARCH PARTICIPANT REGISTRATION AND RANDOMIZATION PROCEDURES

15.2 Research Participant Registration

Confirm eligibility as defined in the section entitled Criteria for Patient/Subject Eligibility.

Obtain informed consent, by following procedures defined in section entitled Informed Consent Procedures.

During the registration process registering individuals will be required to complete a protocol specific Eligibility Checklist.

All participants must be registered in the Clinical Trial Management Systems (CTMS) program at Memorial Sloan Kettering Cancer Center.

15.3 Randomization

No randomization will occur in this study.

16.1 DATA MANAGEMENT ISSUES

A Clinical Research Coordinator (CRC)) will be assigned to the study. The responsibilities of the RSA include project compliance, data collection, abstraction and entry, data reporting, regulatory monitoring, problem resolution and prioritization, and coordinate the activities of the protocol study team. The data collected for this study will be entered into a secure database (Clinical Research Database (CRDB). Source documentation will be available to support the computerized patient record. The principal investigator will maintain ultimate responsibility for the clinical trial.

16.2 Quality Assurance

Weekly registration reports will be generated to monitor patient accruals and completeness of registration data. Routine data quality reports will be generated to assess missing data and inconsistencies. Accrual rates and extent and accuracy of evaluations and follow-up will be monitored periodically throughout the study period and potential problems will be brought to the attention of the study team for discussion and action. Random-sample data quality and protocol compliance audits will be conducted by the study team, at a minimum of two times per year, more frequently if indicated.

16.3 Data and Safety Monitoring

The Data and Safety Monitoring (DSM) Plans at Memorial Sloan-Kettering Cancer Center were approved by the National Cancer Institute in September 2001. The plans address the new policies set forth by the NCI in the document entitled “Policy of the National Cancer Institute for Data and Safety Monitoring of Clinical Trials” which can be found at: http://www.cancer.gov/clinicaltrials/patientsafety/dsm-guidelines/page1

The DSM Plans at MSKCC were established and are monitored by the Office of Clinical Research. The MSKCC Data and Safety Monitoring Plans can be found on the MSKCC Intranet at: http://smskpsps9/dept/ocr/OCR%20Website%20Documents/Clinical%20Research%20Quality%20Assurance%20(CRQA)/MSKCC%20Data%20and%20Safety%20Monitoring%20Plan.pdf

There are several different mechanisms by which clinical trials are monitored for data safety and quality. There are institutional processes in place for quality assurance (e.g., protocol monitoring, compliance and data verification audits, therapeutic response, and staff education on clinical research QA) and departmental procedures for quality control, plus there are two institutional committees that are responsible for monitoring the activities of our clinical trials programs. The Data and Safety Monitoring Committee (DSMC) reports to the Center's Research Council and Institutional Review Board.

During the protocol development and review process, each protocol will be assessed for its level or risk and degree of monitoring required. Every type of protocol (e.g., NIH sponsored, in-house sponsored, industry sponsored, NCI cooperative group, etc.) will be addressed and the monitoring procedures will be established at the time of protocol activation.

17.1 PROTECTION OF HUMAN SUBJECTS

Prior to the enrollment of each patient, the risks, benefits and objectives of the study will be reviewed with the participant, including a discussion of the possible toxicities and side effects. Alternative, non-protocol, treatment options will be discussed with the patient. It will be reviewed that participation in this clinical trial is voluntary and that the patient may withdraw consent at any time. The study is designed with careful safety monitoring for toxicity including physician visits and serial cardiac monitoring. Specific guidelines for symptom management are in place to protect the study participant.

Human Subjects Involvement and Characteristics: All patients at MSKCC who meet the inclusion criteria will be eligible. Up to 12 patients will be enrolled unto the phase 1 portion, and an additional 43 patients will be enrolled onto the Phase 2 portion. Patients eligible will be 18 years of age or older with a KPS of 70% or greater. Both men and women and members of all ethnic groups are eligible for this trial. Pregnant and breast-feeding women are excluded from this study. This protocol does not include children because the number of children is expected to be limited for the patient population expected to be accrued onto this study. Also, the majority of children are already accessed by a nationwide pediatric cancer research network. This statement is based on exclusion 4b of the NIH Policy and Guidelines on the Inclusion of Children as Participants in Research Involving Human Subjects.

Consent process: All patients at MSKCC who meet the inclusion criteria will be eligible. Participation in the trial is voluntary. All patients will be required to sign a statement of informed consent, which must conform to IRB guidelines. The informed consent procedure is described in Section 18.0.

Possible Toxicities/Side-Effects: There are risks associated with treatment as described in Section 11.0; however, patients screened for enrollment will be deemed appropriate for treatment independent of this study.

Benefits: This alternative regimen of Osimertinib and bevacizumab has the potential to prolong progression-free survival, improve the response rate and/or overall survival compared to standard dosing erlotinib in the first-line treatment setting. Patients who progress on combination Osimertinib and bevacizumab can still receive standard, second-line chemotherapy and/or can participate in an alternative clinical trial.

Costs: Patients will be not be charged for bevacizumab. Patients will be charged forphysician visits, routine laboratory tests and radiologic studies required for monitoring their condition. The patients will not be billed for the Osimertinib.

Alternatives: The alternative to this trial would be treatment with erlotinib or afatinib monotherapy or standard cytotoxic chemotherapy.

Confidentiality: Every effort will be made to maintain patient confidentiality. Research and hospital records are confidential. Patients' names and any other identifying information will not be used in reports or publications resulting from this study. Other authorized agencies and appropriate internal personnel (e.g. qualified monitors from MSKCC) and external personnel, the FDA, and/or other governmental agencies) may review patient records as required.

The consent indicates that individualized de identified information collected for the purposes of this study may be shared with other qualified researchers. Only researchers who have received approval from MSK will be allowed to access this information which will not include protected health information, such as the participant's name, except for dates. It is also stated in the Research Authorization that their research data may be shared with other qualified researchers.

Patient safety: Patients are monitored by physicians and oncology nurses who are very familiar with clinical trials. In the case of an adverse reaction, immediate medical attention is available. In the evenings and weekends, we have a 24-hour urgent care facility for outpatients. The PI or co-PI will also be available at all times to organize any necessary intervention.

Monitoring of data to ensure safety: This study is to be monitored by the institutional IRB. This incorporates an independent data and safety monitoring committee established by arrangement with the National Cancer Institute. The analysis of safety will include all patients. Adverse events, including all toxic effects of treatment, will be tabulated individually, and summarized by severity and causality.

17.2 Privacy

MSK's Privacy Office may allow the use and disclosure of protected health information pursuant to a completed and signed Research Authorization form. The use and disclosure of

protected health information will be limited to the individuals described in the Research Authorization form. A Research Authorization form must be completed by the Principal Investigator and approved by the IRB and Privacy Board (IRB/PB).

The consent indicates that individualized de identified information collected for the purposes of this study may be shared with other qualified researchers. Only researchers who have received approval from MSK will be allowed to access this information which will not include protected health information, such as the participant's name, except for dates. It is also stated in the Research Authorization that their research data may be shared with other qualified researchers.

17.3 Adverse Event and Serious Adverse Event (SAE) Reporting

Adverse Events

An AE is any unfavorable and unintended sign, symptom, or disease temporally associated with the use of an investigational medicinal product (IMP) or other protocol-imposed intervention, regardless of attribution.

This includes the following:

- AEs not previously observed in the subject that emerge during the protocol-specified AE reporting period, including signs or symptoms associated with non-small cell lung cancer that were not present prior to the AE reporting period.
- Complications that occur as a result of protocol-mandated interventions (e.g., invasive procedures such as cardiac catheterizations).
- If applicable, AEs that occur prior to assignment of study treatment associated with medication washout, no treatment run-in, or other protocol-mandated intervention.
- Preexisting medical conditions (other than the condition being studied) judged by the investigator to have worsened in severity or frequency or changed in character during the protocol-specified AE reporting period.

Adverse Event Reporting Period

The study period during which AEs and SAEs must be reported begins after informed consent is obtained and initiation of study treatment and ends 30 days following the last administration of study treatment or study discontinuation/termination, whichever is earlier. After this period, investigators should only report SAEs that are attributed to prior study treatment.

Assessment of Adverse Events

All AEs and SAEs whether volunteered by the subject, discovered by study personnel during questioning, or detected through physical examination, laboratory test, or other means will be reported appropriately. Each reported AE or SAE will be described by its duration (i.e., start and end dates), regulatory seriousness criteria if applicable, suspected relationship to the osimertinib and/or bevacizumab (see following guidance), and actions taken.

To ensure consistency of AE and SAE causality assessments, investigators should apply the following general guideline:

Yes

There is a plausible temporal relationship between the onset of the AE and administration of the osimertinib or bevacizumab, and the AE cannot be readily explained by the subject's clinical state, intercurrent illness, or concomitant therapies; and/or the AE follows a known pattern of response to osimertinib and/or bevacizumab; and/or the AE abates or resolves upon discontinuation of the study drug or dose reduction and, if applicable, reappears upon re-challenge.

No

Evidence exists that the AE has an etiology other than the osimertinib or bevacizumab (e.g., preexisting medical condition, underlying disease, intercurrent illness, or concomitant medication); and/or the AE has no plausible temporal relationship to osimertinib and/or bevacizumab administration (e.g., cancer diagnosed 2 days after first dose of study drug).

Expected adverse events are those adverse events that are listed or characterized in the Package Insert (P.I) or current Investigator Brochure (I.B).

Unexpected adverse events are those not listed in the P.I or current I.B or not identified. This includes adverse events for which the specificity or severity is not consistent with the description in the P.I. or I.B. For example, under this definition, hepatic necrosis would be unexpected if the P.I. or I.B. only referred to elevated hepatic enzymes or hepatitis.

For patients receiving combination therapy, causality will be assessed individually for each protocol-mandated therapy.

Eliciting Adverse Events

A consistent methodology for eliciting AEs at all subject evaluation time points should be adopted. Examples of non-directive questions include:

- "How have you felt since your last clinical visit?"
- "Have you had any new or changed health problems since you were last here?"

Specific Instructions for Recording Adverse Events

Investigators should use correct medical terminology/concepts when reporting AEs or SAEs. Avoid colloquialisms and abbreviations.

a. Diagnosis vs. Signs and Symptoms: If known at the time of reporting, a diagnosis should be reported rather than individual signs and symptoms (e.g., record only liver failure or hepatitis rather than jaundice, asterixis, and elevated transaminases). However, if a constellation of signs and/or symptoms cannot be medically characterized as a single diagnosis or syndrome at the time of reporting, it is acceptable to report the information that is currently available. If a diagnosis is subsequently established, it should be reported as follow-up information.

b. Deaths: All deaths that occur during the protocol-specified AE reporting period (see Section I), regardless of attribution, will be reported to the appropriate parties. When recording a death, the event or condition that caused or contributed to the fatal outcome should be

reported as the single medical concept. If the cause of death is unknown and cannot be ascertained at the time of reporting, report “Unexplained Death”

c. Preexisting Medical Conditions: A preexisting medical condition is one that is present at the start of the study. Such conditions should be reported as medical and surgical history. A preexisting medical condition should be re-assessed throughout the trial and reported as an AE or SAE only if the frequency, severity, or character of the condition worsens during the study. When reporting such events, it is important to convey the concept that the preexisting condition has changed by including applicable descriptors (e.g., “more frequent headaches”).

d. Hospitalizations for Medical or Surgical Procedures

Any AE that results in hospitalization or prolonged hospitalization should be documented and reported as an SAE. If a subject is hospitalized to undergo a medical or surgical procedure as a result of an AE, the event responsible for the procedure, not the procedure itself, should be reported as the SAE. For example, if a subject is hospitalized to undergo coronary bypass surgery, record the heart condition that necessitated the bypass as the SAE.

Hospitalizations for the following reasons do not require reporting:

- Hospitalization or prolonged hospitalization for diagnostic or elective surgical procedures for preexisting conditions
- Hospitalization or prolonged hospitalization required to allow efficacy measurement for the study or
- Hospitalization or prolonged hospitalization for scheduled therapy of the target disease of the study

Assessment of Severity of Adverse Events

The adverse event severity grading scale for the NCI CTCAE v4.0 will be used for assessing adverse event severity. Below Table should be used for assessing severity for adverse events that are not specifically listed in the NCI CTCAE.

Adverse Event Severity Grading Scale for Events Not Specifically Listed in NCI CTCAE

Grade	Severity
1	Mild; asymptomatic or mild symptoms; clinical or diagnostic observations only; or intervention not indicated
2	Moderate; minimal, local, or non-invasive intervention indicated; or limiting age-appropriate instrumental activities of daily living [a]
3	Severe or medically significant, but not immediately life-threatening; hospitalization or prolongation of hospitalization indicated; disabling; or limiting self-care activities of daily living [b,c]
4	Life-threatening consequences or urgent intervention indicated d
5	Death related to adverse event [d]

NCI CTCAE = National Cancer Institute Common Terminology Criteria for Adverse Events.

Note: Based on the version of NCI CTCAE v4.0, which can be found at:
http://ctep.cancer.gov/protocolDevelopment/electronic_applications/ctc.htm

a. Instrumental activities of daily living refer to preparing meals, shopping for groceries or clothes, using the telephone, managing money, etc.

b. Examples of self-care activities of daily living include bathing, dressing and undressing, feeding oneself, using the toilet, and taking medications, as performed by patients who are not bedridden.

c. If an event is assessed as a "significant medical event," it must be reported as a serious adverse event

d. Grade 4 and 5 events must be reported as serious adverse events

Pregnancy: If a female subject becomes pregnant while receiving the study drug or within 6 months after the last dose of study drug, or if the female partner of a male study subject becomes pregnant while the study subject is receiving the study drug or within 6 months after the last dose of study drug, a report should be completed and expeditiously submitted to Genentech, Inc. Follow-up to obtain the outcome of the pregnancy should also occur. Abortion, whether accidental, therapeutic, or spontaneous, should always be classified as serious, and expeditiously reported as an SAE. Similarly, any congenital anomaly/birth defect in a child born to a female subject exposed to the study drug should be reported as an SAE.

AEs of Special Interest (AESIs)

AESIs are a subset of Events to Monitor (EtMs) of scientific and medical concern specific to the product, for which ongoing monitoring and rapid communication by the Investigator to the Sponsor is required. Such an event might require further investigation in order to characterize and understand it. Depending on the nature of the event, rapid communication by the trial Sponsor to other parties (e.g., Regulatory Authorities) may also be warranted.

Adverse events of special interest for this study include the following:

- Cases of potential drug-induced liver injury that include an elevated ALT or AST in combination with either an elevated bilirubin or clinical jaundice, as defined by Hy's law:
    - Treatment-emergent ALT or AST > 3 x ULN in combination with total bilirubin >

2 x ULN

- Treatment-emergent ALT or AST > 3 x ULN in combination with clinical jaundice

- Data related to a suspected transmission of an infectious agent by the study drug (STIAMP), as defined below:

Any organism, virus, or infectious particle (e.g., prion protein transmitting transmissible spongiform encephalopathy), pathogenic or non-pathogenic, is considered an infectious agent. A transmission of an infectious agent may be suspected from clinical symptoms or laboratory findings that indicate an infection in a patient exposed to a medicinal product. This term applies only when a contamination of the study drug is suspected

The Avastin Events of Special Interest are:

- Hypertension ≥ grade 3
- Proteinuria ≥ grade 3
- GI perforation, abscesses and fistulae (any grade)
- Wound healing complications ≥ grade 3
- Haemorrhage ≥ grade 3 (any grade CNS bleeding; ≥ grade 2 haemoptysis)
- Arterial thromboembolic events (any grade)
- Venous thromboembolic events ≥ grade 3
- PRES (or RPLS; any grade)
- CHF ≥ grade 3
- Non-GI fistula or abscess ≥ grade 2

Other Special Situations Reports

The following other Special Situations Reports should be collected even in the absence of an Adverse Event and transmitted to Genentech:

- Data related to the Product usage during breastfeeding
- Data related to overdose, abuse, misuse or medication error (including potentially exposed or intercepted medication errors)
- In addition, reasonable attempts should be made to obtain and submit the age or age group of the patient, in order to be able to identify potential safety signals specific to a particular population

Product complaints

A Product Complaint is defined as any written or oral information received from a complainant that alleges deficiencies related to identity, quality, safety, strength, purity, reliability, durability, effectiveness, or performance of a product after it has been released and distributed to the commercial market or clinical trial.

Post-Study Adverse Events

For studies involving collection of survival data the investigator after the end of the adverse event reporting period (defined as 30 days after the last dose of study drug) should report all deaths, (regardless of cause), and any serious adverse event including development of cancer or a congenital anomaly in a subsequently conceived offspring of a female subject who participated in the study that is believed to be related to prior exposure to study drug.

Case Transmission Verification will be performed by both parties during this period (half-yearly) to ensure successful transmission of Single case reports.

Serious Adverse Events

An AE should be classified as an SAE if any of the following criteria are met:

- It results in death (i.e., the AE actually causes or leads to death).
- It is life threatening (i.e., the AE, in the view of the investigator, places the subject at immediate risk of death. It does not include an AE that, had it occurred in a more severe form, might have caused death.).
- It requires or prolongs inpatient hospitalization.
- It results in persistent or significant disability/incapacity (i.e., the AE results in substantial disruption of the subject's ability to conduct normal life functions).
- It results in a congenital anomaly/birth defect in a neonate/infant born to a mother exposed to the IMP.
- It is considered a significant medical event by the investigator based on medical judgment (e.g., may jeopardize the subject or may require medical/surgical intervention to prevent one of the outcomes listed above).

Note: Hospital admission for a planned procedure/disease treatment is not considered an SAE.

SAE reporting is required as soon as the participant starts investigational treatment/intervention. SAE reporting is required for 30-days after the participant's last investigational treatment/intervention. Any event that occur after the 30-day period that is unexpected and at least possibly related to protocol treatment must be reported.

Please note: Any SAE that occurs prior to the start of investigational treatment/intervention

and is related to a screening test or procedure (i.e., a screening biopsy) must be reported.

All SAEs must be submitted in PIMS. If an SAE requires submission to the HRPP office per IRB SOP RR-408 'Reporting of Serious Adverse Events', the SAE report must be submitted within 5 calendar days of the event. All other SAEs must be submitted within 30 calendar days of the event.

The report should contain the following information:

- The date the adverse event occurred
- The adverse event
- The grade of the event
- Relationship of the adverse event to the treatment(s)
- If the AE was expected
- Detailed text that includes the following
    - An explanation of how the AE was handled
    - A description of the participant's condition
    - Indication if the participant remains on the study
- If an amendment will need to be made to the protocol and/or consent form
- If the SAE is an Unanticipated Problem

17.2.1 SAE Reporting to AstraZeneca and Genentech

Any AE from the time the first dose of study treatment is administered through 30 days after the last dose should be reported. AstraZeneca and Genentech are required to evaluate and expedite reporting of serious adverse events to worldwide regulatory authorities; therefore, the appropriate parties, as specified in this section, must be notified immediately (within 24 hours of awareness) regarding the occurrence of any serious adverse event. All investigators participating in ongoing clinical studies with the study medication will receive copies of these reports for prompt submission to their Institutional Review Board (IRB) or Independent Ethics Committee (IEC).

Exchange OF SINGLE CASE REPORTS

Memorial Sloan Kettering Cancer will be responsible for collecting all protocol-defined Adverse Events (AEs)/Serious Adverse Events (SAEs), other Special Situation reports, AESIs and Product Complaints with an AE where the patient has been exposed to the Product via the MSKCC PIMS report form. The completed MSKCC SAE report should be sent to the Genentech contact specified below. Transmission of these reports (initial and follow-up) will be either electronically via email or by fax and within the timelines specified below:

Fax: 650-238-6067
Email: **usds_aereporting-d@gene.com**

All Product Complaints *without* an AE should call via:
PC Hotline Number: (800) 334-0290 (M-F: 5 am to 5 pm PST)

Transmission of these reports (initial and follow-up) will be either electronically or by fax and within the timelines specified below:

Serious Adverse Drug Reactions (SADRs)	*15 calendar days of the awareness date*
Other SAEs	30 calendar days of the awareness date.
Special Situation Reports (Pregnancy) Special Situation Reports (Other)	30 calendar days of the awareness date. 30 calendar days of the awareness date.
Product Complaints	15 calendar days of the awareness date.
AESIs	15 calendar days of the awareness date.

- **Serious Adverse Drug Reactions (SADRs)**
  Serious AE reports that are related to the Product shall be transmitted to Genentech within fifteen (15) calendar days of the awareness date.

- **Other SAEs**
  Serious AE reports that are unrelated to the Product shall be transmitted to Genentech within thirty (30) calendar days of the awareness date.

- **AESIs**
  AESIs shall be forwarded to Genentech within fifteen (15) calendar days of the awareness date.

- **Special Situation Reports**

Pregnancy reports

While such reports are not serious AEs or Adverse Drug Reactions (ADRs) per se, as defined herein, any reports of pregnancy (including pregnancy occurring in the partner of a male study subject), where the fetus may have been exposed to the Product, shall be transmitted to Genentech within thirty (30) calendar days of the awareness date. Pregnancies will be followed up until the outcome of the pregnancy is known, whenever possible, based upon due diligence taken to obtain the follow-up information.

Other Special Situation Reports, as defined above, shall be transmitted to Genentech within thirty (30) calendar days of the awareness date.

- **Product Complaints**

All Product Complaints (with or without an AE) shall be forwarded to Genentech within fifteen (15) calendar days of the awareness date.

A Product Complaint is defined as any written or oral information received from a complainant that alleges deficiencies related to identity, quality, safety, strength, purity, reliability, durability, effectiveness, or performance of a product after it has been released and distributed to the commercial market or clinical trial.

- **AESIs**

AESIs requiring expedited reporting (related or possibly related to Genentech product or where the causality is assessed as unknown or not provided) shall be forwarded to Genentech within fifteen (15) calendar days of the awareness date. Others (non-related to Genentech product) shall be sent within thirty (30) calendar days.

Case Transmission Verification of Single Case Reports

The Sponsor agrees to conduct the Case Transmission verification to ensure that all single case reports have been adequately received by Genentech via Memorial Sloan Kettering Cancer Center emailing Genentech a Quarterly line-listing documenting single case reports sent by Memorial Sloan Kettering Cancer Center to Genentech in the preceding time period.
The periodic line-listing will be exchanged within seven (7) calendar days of the end of the agreed time period. Confirmation of receipt should be received within the time period mutually agreed upon.

If discrepancies are identified, the Sponsor and Genentech will cooperate in resolving the discrepancies. The responsible individuals for each party shall handle the matter on a case-by-case basis until satisfactory resolution. The sponsor shall receive reconciliation guidance documents within the 'Activation Package'.

Following Case Transmission Verification, single case reports which have not been received by Genentech shall be forwarded by Memorial Sloan Kettering Cancer Center to Genentech within five (5) calendar days from request by Genentech.

At the end of the study, a final cumulative Case Transmission Verification report will be sent to Genentech.

GENENTECH REPORTING GUIDELINES

In addition to completing appropriate patient demographic and suspect medication information, the report should include the following information within form:

- Protocol number and title description
- Description of event, severity, treatment, and outcome if known
- Supportive laboratory results and diagnostics
- Investigator's assessment of the relationship of the adverse event to each investigational product and suspect medication

Follow-Up Information

- Additional information may be added to a previously submitted report by any of the following methods:
- Adding to the original report and submitting it as follow-up
- Adding supplemental summary information and submitting it as follow-up with the original form
- Summarizing new information and faxing it with a cover letter including patient identifiers (i.e. D.O.B. initial, patient number), protocol description and number, if assigned, brief adverse event description, and notation that additional or follow-up information is being submitted (The patient identifiers are important so that the new information is added to the correct initial report)

Reporting to Regulatory Authorities, Ethics Committees and Investigators

Genentech as the Marketing Authorization Holder will be responsible for the reporting of individual case safety reports from the study to the regulatory authority in compliance with applicable regulations.

Memorial Sloan Kettering Cancer Center will be responsible for the expedited reporting of safety reports originating from the Study to the Ethics Committees and Institutional Review Boards (IRB), where applicable.

Memorial Sloan Kettering Cancer Center will be responsible for the distribution of safety information to its own investigators, where relevant, in accordance with local regulations.

Memorial Sloan Kettering Cancer Center will be responsible for the distribution of safety information to Site IRB:

MSK Institutional Review Board (IRB) - 212-639-7592.
MSK Patient Representative Department - 212-639-7202.

For questions related to safety reporting, please contact Genentech Drug Safety:

Tel: (888) 835-2555
Fax: (650) 225-4682 or (650) 225-4630

Other Reports

Memorial Sloan Kettering Cancer Center will forward a copy of the Final Study Report to Genentech upon completion of the Study.

STUDY CLOSE-OUT

Any study report submitted to the FDA by the Sponsor-Investigator should be copied to Genentech. This includes all IND annual reports and the Clinical Study Report (final study report). Additionally, any literature articles that are a result of the study should be sent to Genentech. Copies of such reports should be mailed to the assigned Clinical Operations contact for the study:

Fiona Yeh – yehf@mskcc.org

And to Genentech Drug Safety CTV oversight mail box at: ctvist_drugsafety@gene.com

QUERIES

Queries related to the Study will be answered by Memorial Sloan Kettering Cancer Center. However, responses to all safety queries from regulatory authorities or for publications will be discussed and coordinated between the Parties. The Parties agree that Genentech shall have the final say and control over safety queries relating to the Product. Memorial Sloan Kettering Cancer Center agrees that it shall not answer such queries from regulatory authorities and other sources relating to the Product independently but shall redirect such queries to Genentech.

Both Parties will use all reasonable effort to ensure that deadlines for responses to urgent requests for information or review of data are met. The Parties will clearly indicate on the request the reason for urgency and the date by which a response is required.

SAFETY CRISIS MANAGEMENT

In case of a safety crisis, e.g., where safety issues have a potential impact on the indication(s), on the conduct of the Study, may lead to labeling changes or regulatory actions that limit or restrict the way in which the Product is used, or where there is media involvement, the Party where the crisis originates will contact the other Party as soon as possible.

The Parties agree that Genentech shall have the final say and control over safety crisis management issues relating to the Product. Memorial Sloan Kettering Cancer Center agrees that it shall not answer such queries from media and other sources relating to the Product but shall redirect such queries to Genentech.

COMPLIANCE WITH PHARMACOVIGILANCE AGREEMENT / AUDIT

The Parties shall follow their own procedures for adherence to AE reporting timelines. Each Party shall monitor and, as applicable, request feedback from the other Party regarding AE report timeliness in accordance with its own procedures. The Parties agree to provide written responses in a timely manner to inquiries from the other Party regarding AE reports received outside the agreed upon Agreement timelines. If there is any detection of trends of increasing or persistent non-compliance to transmission timelines stipulated in this Agreement, both Parties agree to conduct ad hoc or institute a regular joint meeting to address the issue.
In case of concerns related to non-compliance of processes, other than exchange timelines, with this Agreement, the Parties will jointly discuss and collaborate on clarifying and resolving the issues causing non-compliance. Every effort will be made by the non-compliant Party to solve the non-compliance issues and inform the other Party of the corrective and preventative actions taken.
Upon justified request, given sufficient notice of no less than sixty (60) calendar days, an audit under the provisions of this Agreement can be requested by either Party. The Parties will then discuss and agree in good faith upon the audit scope, agenda and execution of the audit. The requesting Party will bear the cost of the audit.

18.1 INFORMED CONSENT PROCEDURES

Before protocol-specified procedures are carried out, consenting professionals will explain full details of the protocol and study procedures as well as the risks involved to participants prior to their inclusion in the study. Participants will also be informed that they are free to withdraw from the study at any time. All participants must sign an IRB/PB-approved consent form indicating their consent to participate. This consent form meets the requirements of the Code of Federal Regulations and the Institutional Review Board/Privacy Board of this Center. The consent form will include the following:

1. The nature and objectives, potential risks and benefits of the intended study.
2. The length of study and the likely follow-up required.
3. Alternatives to the proposed study. (This will include available standard and investigational therapies. In addition, patients will be offered an option of supportive care for therapeutic studies.)
4. The name of the investigator(s) responsible for the protocol.
5. The right of the participant to accept or refuse study interventions/interactions and to withdraw from participation at any time.

Before any protocol-specific procedures can be carried out, the consenting professional will fully explain the aspects of patient privacy concerning research specific information. In addition to signing the IRB Informed Consent, all patients must agree to the Research Authorization component of the informed consent form.

Each participant and consenting professional will sign the consent form. The participant must

receive a copy of the signed informed consent form.

19.0 REFERENCES

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20.0 APPENDICES

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